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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,210	LUNDGREN-AKERLUND, EVY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5,7-14 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,15 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/7/07, is acknowledged.

2. Claims 1-22 are pending.

3. Claims 5, 7-14 and 16-18 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-4, 6, 15 and 19-22 are under examination as they read on a method of identifying a mammalian mesenchymal stem cell using a marker comprising an integrin alpha 10 chain expressed on the cell surface of a mesenchymal stem cell or intracellular in mesenchymal stem cell as a marker for mammalian mesenchymal stem cells, wherein the expression is detected by an immunoassay.

5. The following new ground of rejection is necessitated by the amendment submitted 8/7/07.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4, 6, 15, and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 3, and 15 are indefinite because they lack a resolution step, a correlation step describing how the results of the assay allow for the determination. It is unclear whether an increase or decrease of expression of alpha 10 would identify MSC.

B. Claim 15 is indefinite because the claim is missing the contacting step. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination.

8. In view of the amendment filed on 8/7/07, only the following rejection is remained.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-4, 6, 15 stand and new claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method of using a marker comprising an integrin alpha 10 chain expressed on the cell surface of a mesenchymal stem cell or intracellular in a mesenchymal stem cell as a marker for mammalian mesenchymal stem cells, wherein said method comprises the steps of a) providing a sample comprising a mesenchymal stem cells, and b) contacting the sample with a molecule which specifically binds integrin alpha 10 chain or integrin alpha 10 chain in claim 1, wherein the integrin alpha 10 chain is expressed as a heterodimer in combination with an integrin beta 1 chain in claim 2, or a method for identifying a mammalian a mammalian mesenchymal stem cell in claim 3, or a method for identification of a mammalian mesenchymal stem cell, comprising ustilizing a marker comprising an integrin alpha chain expressed on the cell surface of a mesenchymal stem cell or intracellular in a mesenchymal stem cell in claim 15 for the same reasons set forth in the previous Office Action mailed 3/13/07.

Applicant's arguments, filed 8/7/07, have been fully considered, but have not been found convincing.

Regarding the control in example 3 of the specification, Applicant submits that the bone marrow stormal cells cultured on plastic yield a heterogenous cells population containing MSCs as well as more differentiated derivative cells and monocytes/macrophages. The ratio of the various cell types depends on the length of conditions of in vitro culture. Applicant submits that MSCs can be enriched by addition of EGF-2 to in vitro bone morrow stromal cell cultures. Enrichment occurs because FGF-2 is a potent mitogen for MSC.

However, the purpose of the claimed method of utilizing anti-α10 antibody is to identify/marker for MSC in a heterogenous cell population containing MSCs. Further, the claim recites a sample "comprising a MSC". If applicant intends to identify known MSCs, that defeats the purpose of anti-α10 antibodies being a marker for MSC.

Regarding Bianchi et al, Applicant submits that EGF-2 supplementation of primary bond marrow stromal cell cultures in vitro selects for the survival of multipotent MSCs, which are capable of differentiating into various different cell types. Applicant points that in Tsutsumi et al, FGF-2 has similar effects on proliferation and self-renewal of MSCs isolated from other sources such as adipose tissue.

Again, Applicant is identifying MSCs from only hMSCs sample (FGF-2 stimuation). As is evidenced by Applicant's arguments and the specification. Applicant argues that FGF-2 has effect on proliferation and self-renewal of MSCs and that "cells" or "the cells" as used in Example 3, refers to the FGF2 treated MSCs. The specification at Example 3 discloses that 96%

of the cells treated with FGF-2 express the integrin alpha10 (lower panel, Figure 4b). In Example 3, human bone marrow cells were cultured with or without FGF-2 and the cells were analyzed by FACS using a monoclonal antibody to alpha10 as a means to analyze the cells, however, only the results of the cells that were cultured with FGF-2 were shown, no data were shown on the cells that were cultured without FGF-2. Regarding the a subset of cells enriched in pluripotent mesenchymal precursors; the literature is full of articles that indicates that the addition of FGF-2 to hMSCs is used for the retention of both proliferative capacity and osteogenic differentiation potential in vitro and in vivo (see Mauney et al, page 792). Walsh et al teaches that based on the observed increase in the expression of the developmental markers STRO-1 and alkaline phosphatase (AP), a major target for the action of FGF-2 appears to be the more primitive cells of the osteoblast lineage (see abstract).

Applicant submits that there is no scientific basis for the Office's contention that the cells in the control (Figure 4a) are different from the cells in the analyszed sample (Figure 4b) with respect to integrin $\alpha 10$ expression.

The Examiner agrees with applicant statement, however, in order for the specification to show that the integrin $\alpha 10$ is a marker for MSC, the additional control which was performed and analyzed by FACS on cultured human bone marrow cells without FGF-2 treatment, but the results were not shown. However, such control only would provide information that the $\alpha 10$ antibody identify multipotency MSC, because only MSC and derivative cells (the starting material) have the capacity to adhere to the plastic. A good control would be using anti-$\alpha 10$ antibody to isolate MSC form human bone marrow sample and then determine the capacity of the isolated MSC proliferation and multipotency.

Applicant submits that the Office mischaracterizes Murdoch et al with respect to the teachings that the FGF-2 treated MSCs represent a special subpopulation of MSCs that is characterized by a robust chondrogenic response.

However, the activity of FGF-2 on MSCs response is not clear in view of the instant disclosure and the unpredictability of the art on the effect of FGF-2 on MSCs. Murdoch et al (European Cells and Materials 6(Suppl. 2): 17 2003, of record) teaches that isolation of human bone marrow mesenchymal cells in medium containing FGF2 gave a cell population with a robust chondrogenic response when tested in the pellet culture system. This method gave a similar result in all different donor samples tested to date, whereas cells isolated from the same samples without added FGF2 were not overtly chondrogenic (see Results in particular). It appears that using FGF-2 as a mitogen for self-renewal of MSCs is unpredictable. There are contradictory results regarding the activity of FGF-2 effect on MSCs. Mauney et al and references cited therein (Tissue Engineering, 11(5/6):787-802, 2005), teach that addition of FGF-2 during ex vivo expansion of human MSCs has been demonstrated as a strategy for the retention of both proliferative capacity and osteogenic differentiation potential in vitro and in vivo (see page 792). Bianchi et al (cited by Applicant) teaches that FGF-2 supplementation of primary bone marrow stromal cell cultures in vitro selects for the survival of multipotent MSCs, which are capable of

differentiating into various different cell types, including the three major derivatives. Applicant submits that FGF-2 activity on the MSCs results in MSCs proliferation and multipotency. Due to the contradictory activity of the FGF-2, undue experimentation would be required of the skilled artisan to determine the effect of FGF-2 on any particular cell response in view of the instant disclosure.

Applicant argues that the Office further stated that "it is not clear that osteogenic, myogenic, marrow stroma, tendogenic/ligamentogenic cells of the hMSC express alpha10 integrin," apparently to support the contention that MSCs do not express integrin α10 and therefore the claimed method of utilizing integrin α10 as a marker for MSCs can not work. Applicant submits that osteogenic, myogenic, marrow stroma, tendogenic/ligamentogenic cells are not MSCs since they are differentiated cells. They are differentiated derivatives of MSCs. Hence, these cells do not have to express integrin α10 for the claimed method to be successful.

Contrary to applicant's submision, in order for α10 to be a marker for MSCs, it has to be suitable to distinguish MSCs from chondrocytes, osteoblasts among others. since the prior art and the specification indicate that α10 can identify other cells such as chondrocytes and the the effect of FGF-2 on MSCs may result in a subpopulation with a specific differentiation potential, it is curtial to know whether such cells express α10 integrin. The specification on page 1, lines 36-39 discloses that alpha10beta1 is expressed on chondrocytes (MSC deriveative). The WO 99/51639 teaches the use of binding entities specific for α10 as a marker or target molecule of cells cells expressing integtin subunit α10, wherein said cells is osteoblasts (MSC) see published claims 28, 43, 51, 34, 52, 60, in particular). In order for α10 to be a marker for MSCs, it has to be suitable to distinguish MSCs from chondrocytes and osteoblasts.

Applicant submits that surface-expressed integrin α10 can be used as a marker to distinguish MSCs from all cells that do not express this integrin chain. Applicants further submit that their results also revealed that surface-expression of integrin α10 is detectable only on very few cell types besides MSCs, i.e. the expression pattern is highly restricted, and that its expression correlates with multipotency of MSCs. Integrin α10 is the only marker known to Applicant that displays such a correlation, rendering this marker highly valuable for the detection and isolation of multipotent MSCs.

However, it cannot be seen how the anti-α10 antibodies would act as a marker for MSC in a heterogenous cell population containing MSCs, chondrocytes and osteoblasts (see WO 99/51639 of record, Camper et al., IDS ref. and the specification page 1, lines 36-39).

Applicant submits that the Office further cited WO99/51639 (of record) as teaching that integrin αl0 is expressed in aorta (normal nonatherosclerotic artery). Office Action, page 4. Applicant notes that this study also analyzed exclusively integrin αl0 mRNA levels but not integrin αl0 protein levels. Hence, for the reasons outlined above the described results may not correlate to integrin αl0 protein expression in aorta.

However, the `639 publication teaches that the isolated integrin subunit alpha10 can be used as a marker or target molecule for cells during pathological conditions such as atherosclerosis (see page 9, lines 11-37 in particular). Further, 2005/0255182 A1 publication teaches a method for detecting atherosclerotic plaque comprising determine the amount of integrin alpha10 chain using antibody. The `182 publication establishes the correlation between the mRNA level and the protein level of α10 on the atherosclerotic plaque.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 2, 2006

Maher Haddad

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